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ORIGINAL ARTICLE

Ratio of hepatic arterial flow to recipient body weight predicts biliary complications after deceased donor liver transplantation

Peter T. W. Kim, Giovanna Saracino, Linda Jennings, Michael Ramsay, Gregory J. McKenna, Giuliano Testa, Tiffany L. Anthony, Nicholas Onaca, Richard M. Ruiz, Robert M. Goldstein, Marlon F. Levy & Goran B. Klintmalm

Simmons Transplant Institute, Baylor University Medical Center, Dallas, TX, USA

Abstract

Objectives: Adequate hepatic arterial (HA) flow to the bile duct is essential in liver transplantation. This study was conducted to determine if the ratio of directly measured HA flow to weight is related to the occurrence of biliary complications after deceased donor liver transplantation.

Methods: A retrospective review of 2684 liver transplants carried out over a 25-year period was performed using data sourced from a prospectively maintained database. Rates of biliary complications (biliary leaks, anastomotic and non-anastomotic strictures) were compared between two groups of patients with HA flow by body weight of, respectively, <5 ml/min/kg ($n = 884$) and ≥5 ml/min/kg ($n = 1800$).

Results: Patients with a lower ratio of HA flow to weight had higher body weight (92 kg versus 76 kg; $P < 0.001$) and lower HA flow (350 ml/min versus 550 ml/min; $P < 0.001$). A lower ratio of HA flow to weight was associated with higher rates of biliary complications at 2 months, 6 months and 12 months (19.8%, 28.2% and 31.9% versus 14.8%, 22.4% and 25.8%, respectively; $P < 0.001$).

Conclusions: A ratio of HA flow to weight of < 5 ml/min/kg is associated with higher rates of biliary complications. This ratio may be a useful parameter for application in the prevention and early detection of biliary complications.

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Correspondence

Goran B. Klintmalm, Simmons Transplant Institute, Baylor University Medical Center, 3410 Worth Street, Suite 950, Dallas, TX 75246, USA. Tel: + 1 214 820 1757. Fax: + 1 214 818 6491. E-mail: gorank@baylorhealth.edu

Introduction

Biliary complications are common after liver transplantation and continue to represent a source of major morbidity.[1,2] Early complications are usually attributable to technical problems, whereas longterm complications are thought to be caused by an impaired blood supply to the bile duct. The hepatic artery (HA) has been considered the major blood supply to the bile duct.[3–5] A recent study outlined the relationship between the HA buffer response,[6] the mechanism by which the HA can increase its blood flow in response to a decreased portal flow, and the incidence of early biliary complications.[7] Many of the published studies on HA flow have focused on the relationship between the hepatic blood flow and arterial complications.[8,9] Since the inception of the present authors' liver transplantation programme, the intraoperative flows of the post-perfusion portal vein and HA have been measured at this centre. The present study reports on the ratio of directly measured HA flow to patient body weight and the relationship of this ratio to the occurrence of biliary complications after deceased donor liver transplantation.

This study was presented at the Annual Meeting of the AHPBA, 19-23 February 2014, Miami, Florida.

Materials and methods

Patients and study design

The study was approved by the institution's research ethics board. The study included 3014 patients who underwent liver transplantation as their first graft during the period from January 1986 to April 2011. Retransplants were excluded. Of these patients, 2684 had complete flow data and 330 were excluded because complete flow data were lacking. Deceased donor liver transplantation was performed in 2498 (93.1%) patients, using organs donated after cardiac death in 189 (7.0%) patients.

Surgical technique

Liver transplantation was performed using either the caval interposition technique or the piggyback technique according to the surgeon's preference. When caval interposition was performed, a portal and systemic veno–veno bypass technique was used at the discretion of the surgeon. The graft was flushed with 1 l of albumin containing lactated Ringer's solution prior to reperfusion.

Flow measurement techniques

Flow measurements were obtained just prior to abdominal closure using the Cliniflow II FM701D Electromagnetic Blood Flow Meter (Carolina Medical Electronics, Inc., East Bend, NC, USA). The same equipment and method of measurement were used throughout the entire study period. Hepatic artery flow, portal vein flow and cardiac output at the time of the measurement (by Swan–Ganz catheter) were recorded in a prospectively maintained database. In instances in which vasospasm was suspected, a vasodilator such as papaverine was used to relax the vessel.

Determination of significant flow parameters

The variable selection and model-building strategy was based on a combination of stepwise regression, the Akaike information criterion, and the best subset selection. Using this method, the following flow variables were assessed for their significance: HA flow (ml/min); portal vein flow (ml/min); HA flow by body weight (ml/min/kg); portal vein flow by body weight (ml/min/kg); the ratio of HA flow to portal vein flow; the ratio of HA flow to cardiac output, and the ratio of portal vein flow to cardiac output. The ratio of HA flow to body weight was identified as the variable that was most likely to be significant.

Determination of significant cut-off values

An optimal cut-off point for the ratio of HA flow to body weight was determined by weighing the cost of a loss of sensitivity against the gain of an increase in specificity in conjunction with various accuracy and error measures, and choosing a cut-off value at which the Youden index and other accuracy measures would be maximized and the error measures would be minimized. Based on this method, a cut-off of 5 ml/min/kg of HA flow by body weight was identified, and patients were divided into two groups consisting of: (i) those with an HA flow by body weight of ≥5 ml/min/kg (n = 1800), and those with an HA flow by body weight of < 5 ml/min/kg (n = 884).

Definitions

Biliary complications were defined as the following: biliary strictures; ischaemic strictures; biliary obstruction; anastomotic leak, and bile peritonitis.

Statistics

Descriptive results for continuous variables were presented as medians and quartiles (25th, 75th), whereas categorical demographic and clinical characteristics were summarized as percentages. Group comparisons were established using the Kruskal–Wallis test and the Wilcoxon two-sample test for continuous variables. Categorical variables were compared with Fisher's exact test (two-sided) and with the likelihood ratio chi-squared test for larger tables. Time to biliary complication was calculated for all subjects from the time of liver transplantation to the date of the first biliary complication. Subjects without complications were censored at the date of last follow-up or death. Patient and graft survival and the time to the first biliary complication were estimated with the Kaplan–Meier product-limit method and were compared with the log-rank statistic. A P-value of ≤0.05 was considered to indicate statistical significance. All analyses were performed using SAS Version 9.1.3 (SAS Institute, Inc., Cary, NC, USA).

Results

Demographics

As illustrated in Table 1, the group with a lower HA flow-to-weight ratio had a higher body weight, body mass index and body surface area. This group also had lower total HA flows (350 ml/min versus 550 ml/min; P < 0.001) (Table 2).

Biliary complications

The cumulative incidence of biliary complications after liver transplantation was significantly higher in the group of patients with a lower HA flow-to-weight ratio, as illustrated in Fig. 1. The incidence of non-anastomotic ischaemic strictures was 1.6%. This group of patients had higher rates of biliary complications at 2 months, 6 months and 12 months (19.8%, 28.2% and 31.9% versus 14.8%, 22.4% and 25.8%, respectively; P < 0.001). Although the overall HA complication rates were similar in both groups, the rate of HA thrombosis was higher in the group with a lower ratio of HA flow to body weight. Furthermore, there was no difference in HA stenosis between the groups (Table 3).

To examine the impact of the different eras of liver transplantation, flow-dependent biliary complications were analysed in two eras: early (1986–1996), and late (1997–2011). As illustrated in Figs 2 and 3, there was no difference in biliary complications between the two groups in the early era (P = 0.648), but there was a significant difference in biliary complications between the two groups in the later era (P < 0.001).

Discussion

The results of this study suggest that the incidence of biliary complications after deceased donor liver transplantation is associated with the ratio of HA flow to recipient body weight. It is well known that the HA is the sole blood supply to the bile duct and that events which lead to a decrease in HA flow to the bile duct can

Table 1 Demographic parameters in patients submitted to deceased donor liver transplantation

Variable	HA/weight ≥ 5 ml/min/kg (*n* = 1800)	HA/weight < 5 ml/min/kg (*n* = 884)	*P*-value
Age, years, median (range)	50 (44–57)	51 (45–57)	0.12
Sex, M/F, *n*	1017/783	610/274	<0.001
Weight, kg, median (range)	76 (64–88)	92 (79–106)	<0.001
BMI, kg/m^2, median (range)	25.7 (22.6–29.6)	29.9 (26.0–33.9)	<0.001
BSA, m^2, median (range)	1.9 (1.7–2.1)	2.1 (1.9–2.3)	<0.001
Primary diagnosis, *n* (%)			
HCV ± EtOH	468 (26.0%)	287 (32.5%)	<0.001
EtOH	174 (9.7%)	121 (13.7%)	
NASH	203 (11.3%)	126 (14.3%)	
HCC	347 (19.3%)	147 (16.6%)	
PSC/PBC/AIH	372 (20.7%)	89 (10.1%)	
FHF	65 (3.6%)	26 (2.9%)	
Others	171 (9.5%)	88 (10.0%)	
MELD score, median (range)	16 (12–21)	17 (13–23)	<0.001
CIT, Hours, median (range)	8.4 (6.3–10.9)	8.4 (6.4–11.1)	0.31
Donor age, years, median (range)	35 (21–49)	42 (25–55)	<0.001

HA, hepatic artery; M, male; F, female; BMI, body mass index; BSA, body surface area; HCV, hepatitis C virus; EtOH, alcoholic cirrhosis; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; FHF, fulminant hepatic failure; MELD, Model for End-stage Liver Disease; CIT, cold ischaemic time.

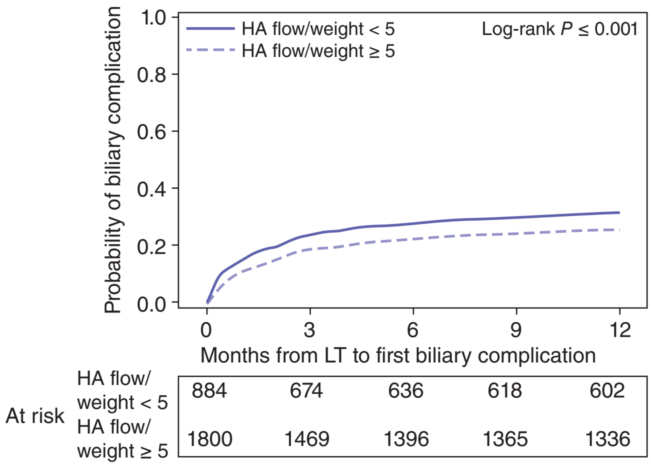

Figure 1 Cumulative incidence of biliary complications by the ratio of hepatic arterial (HA) flow to body weight after deceased donor liver transplantation (LT) in liver transplant recipients operated during 1986–2011

result in biliary complications. The results of the present study appear to demonstrate this principle in that common biliary complications related to a lack of blood supply were higher in patients with lower HA flow calibrated to patient body weight. This impact was seen early in the postoperative course and was sustained in the long term, implying that intraoperative findings with reference to haemodynamics may be an indicator of what may happen to the vascular supply of the liver in the long term.

To the best of the authors' knowledge, this study is the first to demonstrate a relationship between a measured HA flow-to-weight ratio and longterm biliary complications after deceased donor liver transplantation. A recent study by Hashimoto *et al.* demonstrated a relationship between impaired HA buffer response (defined by impaired buffer capacity) and early (within 60 days of liver transplant) biliary complications, but this relationship was not sustained longterm.[7] In the same study, other than an impaired HA buffer response, other flow parameters such as basal HA flow and portal vein flow did not have any impact on biliary complications.[7]

The current study is unique in that the recipients' weight appears to have played a role in the development of biliary complications. There are a few potential reasons for this finding. It is possible that increased body weight itself may be a risk factor in outcomes after liver transplantation and that the combination of a decreased HA flow and higher recipient body weight have a synergistic effect on the occurrence of biliary complications. Obesity has been associated with a higher rate of infectious complications,[10] a longer intensive care unit stay,[10,11] and a greater incidence of respiratory failure.[12] It has also been associated with a higher rate of biliary complications requiring endoscopic and percutaneous intervention.[11]

Table 2 Intraoperative flow and haemodynamic parameters in patients submitted to deceased donor liver transplantation

Variable	HA/weight ≥5 ml/min/kg (*n* = 1800)	HA/weight <5 ml/min/kg (*n* = 884)	*P*-value
HA flow, ml/min, median (range)	550 (454–720)	350 (280–420)	<0.001
HA flow-to-weight ratio, median (range)	7.2 (6.0–9.4)	4.0 (3.3–4.5)	<0.001
Transfusions, units, median (range)			
Red blood cells	4 (2–7)	4 (2–7)	0.34
Fresh frozen plasma	5 (2–9)	6 (3–9)	<0.001
Platelets	1 (0–4)	1 (0–6)	<0.001
Cryoprecipitate	1 (0–10)	2 (0–10)	0.02
Warm ischaemic time, min, median (range)	53 (45–63)	54 (45–65)	0.03

HA, hepatic artery.

Table 3 Postoperative complications in patients submitted to deceased donor liver transplantation

Variable	HA/weight ≥5 ml/min/kg (*n* = 1800)	HA/weight <5 ml/min/kg (*n* = 884)	*P*-value
Hepatic arterial complications, *n* (%)	220 (12.2%)	123 (13.9%)	0.22
Hepatic artery thrombosis, *n* (%)	55 (3.1%)	51 (5.8%)	0.001
Hepatic artery stenosis, *n* (%)	154 (8.6%)	66 (7.7%)	0.46
Acute cellular rejection (0–3 months), *n* (%)	841 (46.7%)	385 (43.6%)	0.13
Cytomegalovirus infections (0–3 months), *n* (%)	364 (20.2%)	152 (17.2%)	0.07
Chronic rejection, *n* (%)	81 (4.5%)	24 (2.7%)	0.03
Ischaemic cardiac events, *n* (%)	48 (2.7%)	31 (3.5%)	0.22

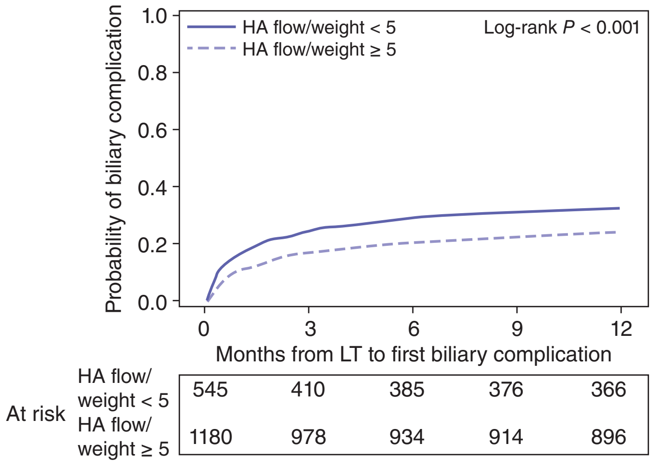

Figure 3 Cumulative incidence of biliary complications by the ratio of hepatic arterial (HA) flow to body weight after deceased donor liver transplantation (LT) in liver transplant recipients operated during 1997–2011

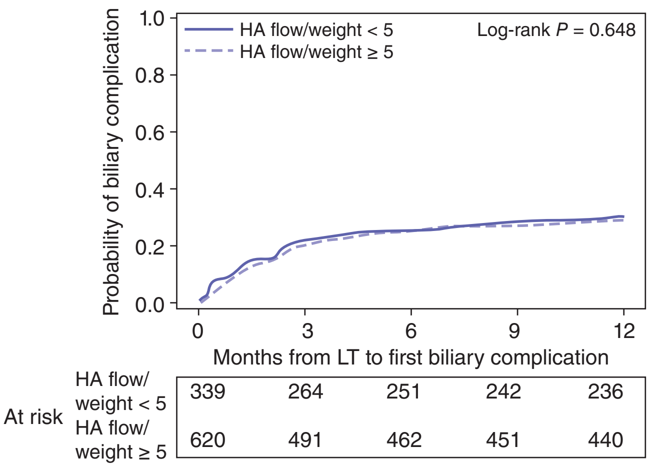

Figure 2 Cumulative incidence of biliary complications by the ratio of hepatic arterial (HA) flow to body weight after deceased donor liver transplantation (LT) in liver transplant recipients operated during 1986–1996

Another possible explanation is that obesity may have an effect on portal blood flow to the liver in that increased portal flow is associated with decreased HA flow. This is suggested by clinical and experimental evidence that links obesity to portal hypertension in the absence of significant hepatic fibrosis.[13,14] Francque *et al*. reported that steatosis in the liver alone causes portal hypertension in the absence of a significant degree of fibrosis.[14] In addition, markers of visceral fat accumulation were significantly associated with hepatic steatosis and portal hypertension. The same group correlated the portal hypertension observed in this scenario to splanchnic vasodilation in a rat model.[13] Furthermore, in steatotic livers, a decrease in HA flow has been observed.[15,16]

The present study is limited by the fact that complete flow data were not available for all of the patients who underwent deceased donor liver transplantation at the study centre and, as a result, some cases were excluded from the analyses. It is possible that this may have introduced a selection bias. In addition, this study covered a relatively long period of 25 years and practices of transplantation may have changed over this time period. This was addressed by dividing the observations into those pertaining to each of two eras. The impact of a low flow-to-weight ratio on biliary complications was observed in the later era only. The reason for this observation is multifactorial. As the field evolved over time, approaches to and management of liver transplant at the study centre also developed.

The potential application of an observation of a low HA flow-to-weight ratio in the daily practice of liver transplant surgeons is two-fold. Intraoperatively, a lower HA flow may represent a clue to an underlying arterial problem and lower the surgeon's threshold for the further assessment of technical problems. In addition, the surgeon may consider technical manoeuvres such as splenic artery ligation to redirect arterial flow to the HA when low HA flow is observed in an obese patient. Postoperatively, in patients with a low HA flow-to-body weight ratio, surgeons may have a lower threshold for investigating the biliary anastomosis.

Conclusions

An HA flow to body weight of < 5 ml/min/kg is associated with a higher rate of biliary complications after deceased donor liver transplantation. This flow parameter is one of many factors contributing to the occurrence of these common postoperative complications after liver transplantation. This ratio may be a useful parameter to consider in the care of such patients for the potential prevention or early detection of biliary complications.

Conflicts of interest

None declared.

References

1. Thethy S, Thomson B, Pleass H, Wigmore SJ, Madhavan K, Akyol M *et al*. (2004) Management of biliary tract complications after orthotopic liver transplantation. *Clin Transplant* 18:647–653.
2. Hampe T, Dogan A, Encke J, Mehrabi A, Schemmer P, Schmidt J *et al*. (2006) Biliary complications after liver transplantation. *Clin Transplant* 20 (Suppl. 17):93–96.
3. Elias H, Petty D. (1953) Terminal distribution of the hepatic artery. *Anat Rec* 116:9–17.
4. Takasaki S, Hano H. (2001) Three-dimensional observations of the human hepatic artery (arterial system in the liver). *J Hepatol* 34:455–466.
5. Northover JM, Terblanche J. (1979) A new look at the arterial supply of the bile duct in man and its surgical implications. *Br J Surg* 66:379–384.
6. Eipel C, Abshagen K, Vollmar B. (2010) Regulation of hepatic blood flow: the hepatic arterial buffer response revisited. *World J Gastroenterol* 16:6046–6057.
7. Hashimoto K, Miller CM, Quintini C, Aucejo FN, Hirose K, Uso TD *et al*. (2010) Is impaired hepatic arterial buffer response a risk factor for biliary anastomotic stricture in liver transplant recipients? *Surgery* 148:582–588.
8. Abbasoglu O, Levy MF, Testa G, Obiekwe S, Brkic BS, Jennings LW *et al*. (1998) Does intraoperative hepatic artery flow predict arterial complications after liver transplantation? *Transplantation* 66:598–601.
9. Molmenti EP, Levy MF, Molmenti H, Casey D, Fasola CG, Hamilton WM *et al*. (2002) Correlation between intraoperative blood flows and hepatic artery strictures in liver transplantation. *Liver Transpl* 8:160–163.
10. Hakeem AR, Cockbain AJ, Raza SS, Pollard SG, Toogood GJ, Attia MA *et al*. (2013) Increased morbidity in overweight and obese liver transplant recipients: a single-centre experience of 1325 patients from the United Kingdom. *Liver Transpl* 19:551–562.
11. LaMattina JC, Foley DP, Fernandez LA, Pirsch JD, Musat AI, D'Alessandro AM *et al*. (2012) Complications associated with liver transplantation in the obese recipient. *Clin Transplant* 26:910–918.
12. Nair S, Cohen DB, Cohen MP, Tan H, Maley W, Thuluvath PJ. (2001) Postoperative morbidity, mortality, costs, and longterm survival in severely obese patients undergoing orthotopic liver transplantation. *Am J Gastroenterol* 96:842–845.
13. Francque S, Wamutu S, Chatterjee S, Van Marck E, Herman A, Ramon A *et al*. (2010) Non-alcoholic steatohepatitis induces non-fibrosis-related portal hypertension associated with splanchnic vasodilation and signs of a hyperdynamic circulation *in vitro* and *in vivo* in a rat model. *Liver Int* 30:365–375.
14. Francque S, Verrijken A, Mertens I, Hubens G, Van Marck E, Pelckmans P *et al*. (2011) Visceral adiposity and insulin resistance are independent predictors of the presence of non-cirrhotic NAFLD-related portal hypertension. *Int J Obes (Lond)* 35:270–278.
15. Seifalian AM, Chidambaram V, Rolles K, Davidson BR. (1998) *In vivo* demonstration of impaired microcirculation in steatotic human liver grafts. *Liver Transpl Surg* 4:71–77.
16. Seifalian AM, Piasecki C, Agarwal A, Davidson BR. (1999) The effect of graded steatosis on flow in the hepatic parenchymal microcirculation. *Transplantation* 68:780–784.